DECLARATION

In the United States Patent Office

In re application of

Gerhard HÖFLE, Wolfgang RICHTER

Application no. 10/520,769

International filing date: July 15, 2003

Title: Novel macrocycles for the treatment of cancer

1. I, Prof. Dr. Ludger Wessjohann, of Otto-Kanning-Str. 32, D-06120 Halle (Saale), Germany, am Director of the department of Bioorganic Chemistry of the Leibniz Institute of Plant Biochemistry, Halle (Saale), Germany. I am also a chemist and my field of research and expertise is in the area of organic, bioorganic and medicinal chemistry. I am also the co-author of several publications relating to the synthesis of epothilone derivatives and a teacher of medicinal chemistry courses.

I have carefully studied and fully understood the prior art references

a) K. C. Nicolaou, Frank Roschangar, and Dionisios Vourloumis, Chemical Biology of Epothilones, Angew. Chem. Int. Ed. 1998, 37, 2014-2045

b) George A. Patani and Edmond J. LaVoie, Bioisosterism: A Rational Approach in Drug Design, Chem. Rev. 1996, 96, 3147-3176

2. The subject matter of claim 1 pertains to epothilone derivatives wherein the CO group at C5 has been replaced by a SO group. These compounds show a similar activity range against certain cancer cell lines (e.g. cell lines MCF-7 and KB-31).

   For the reasons laid out below, I do not share the Examiner's opinion that the present invention would have been obvious in view of the presented prior art references.

3. In column 1 on page 3167 of Patani et al., a series of benzophenone dicarboxilic acids as potential inhibitors of LTB_4 are discussed. In Table 39 it is shown that the sulfur linked derivatives 82d to 82f show a similar activity as the carbonyl derivative. From these findings, Patani concludes that that this portion of the molecules is not critically involved in LTB_4 receptor binding.
   (cf.: "*However, the lack of any significant difference in activity upon replacement of the carbonyl with either a thioether, sulfoxide or sulfone, which differ widely with respect to their polarities and hybridisation, suggests that this portion of the molecule is not critically involved in LTB_4 receptor binding.*")

4. Thus, Patani clearly teaches that if in a non-critical part of a molecule, CO is replaced by SO, he would expect no significant change in the biological activity. On the other hand, if in a part of a molecule which is relevant for the

biological activity, CO is replaced by SO, Patani would expect major changes in the biological activity. (cf.: "*This example illustrates how bioisosteric analogues can be used to identify those sites on the drug which have a major impact on the interaction that occurs with the pharmacophore.*" p. 3167, col. 1-2)

5. Nicolaou et al. teaches on page 2040 that a loss of activity was observed when the C5 ketone was reduced or when the C5 substituent was removed. This clearly shows, that the CO-moiety at the C5 position is of great importance for the activity of epothilone derivatives.

   Although Nicolaou fails to show any compound or activities of compounds with a reduced ketone in the C5 position, the person of ordinary skill would nevertheless determine that this position is essential for the biological activity of the compound, since there is no reason to question the information given in Nicolaou et al.

6. Therefore, if at C5 of an epothilone derivative, CO is replaced by SO, the person skilled in the art would expect, that this replacement will have a great influence on the biological activity of the corresponding derivative. Consequently, the person skilled in the art could not expect that the molecules of the present invention show similar activities when compared with compounds carrying a CO group at C5.

7. Moreover, due to the different binding angles (120° in a R-CO-R molecule and less than 100° in a R-SO-R molecule) and size the person skilled in the art would expect that

the replacement of CO by SO has a great influence on the conformation of a macrocycle and therefore, the person skilled in the art would expect that this also has a great influence on the biological activity of the corresponding derivative. As is apparent from the data given in the enclosed declaration by Dr. Wolfgang Richter, this is not the case in the epothilone derivatives of the present invention.

8. In addition, it is to be noted that in a R-CO-R molecule, all groups lie within one plane whereas in a R-SO-R molecule the oxygen is positioned above or below the plane created by the R-S-R group. Therefore, the person skilled in the art would expect that the activity of epothilone derivatives wherein the CO moiety at position C5 is replaced by a SO moiety, the activity of the resulting derivatives would rather be comparable with the activity of a derivative carrying an OH group at C5. As discussed above, Nicolaou et al. teaches that this derivative shows a loss of activity.

9. In a more general sense, sulfide -S- based on standard textbook knowledge, is of a similar electronegativity as carbon and thus often can be used as electronic isoster of a CH_2-group. However, that is by far not true in medicinal chemistry for the following reasons: the bond distance and polarizability is larger, two electron pairs are present, and most important: such sulfides are usually not metabolically stable, they get readily involved in redox reaxtions. This differnce is also true for sulfoxides, which have one electron pair at sulfur, and usually are also easily reduced and oxidized. Sulfoxide has a totally

different behavior than a C=O group with respect to its binding properties, it is a stronger hydrogen-bond acceptor with a totally different directionality, as pointed out above. (Please note that the ancient practice of writin sulfoxides as S=O with a double bond is wrong and gives a wrong impression). Also sulfoxide has a different conformational influence on its neighboring moieties, a different Lewis-basicity and dipole moment, and a very different reactivity.

10. In summary, the invention of the present application could neither be predicted nor has it been obvious from the individual teachings or, as argued by the examiner, from a combination of the teachings of the prior art references Nicolaou et al. and Patani et al. Thus it is believed that the above named application is based on an inventive step with respect to the prior art.

11. I further declare, that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that wilful false statements may jeopardize the validity of the application or any patent issuing thereon.

28.04.2008

Enclosures
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Title: Novel Macrocycles for the treatment of cancer

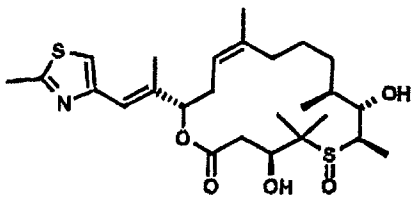
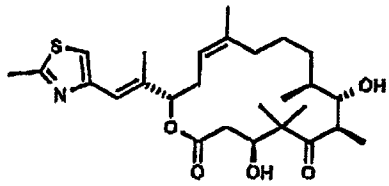
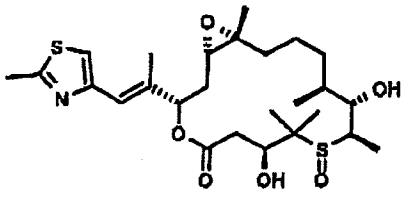
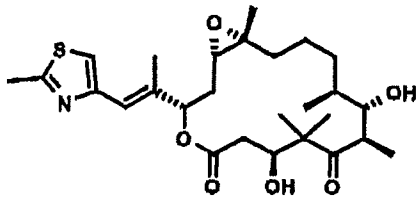
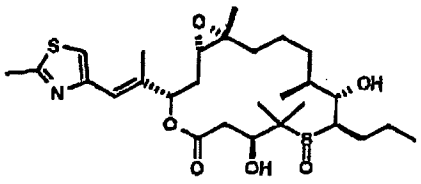
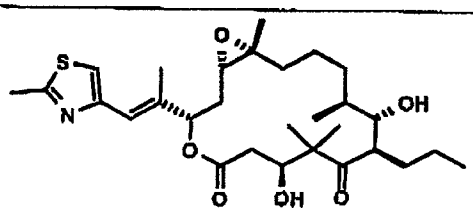
I, Dr. Wolfgang Richter, of Leharstrasse 25, 81243 München, Germany, am Managing Director of R&D-Biopharmaceuticals GmbH, Munich, Germany. I am also a chemist and my field of research and expertise is in the area of organic and medicinal chemistry.

I herby declare that the following experimental data was either obtained under the advice of Dr. Sybille Hess, Head of Biology, Morphochem AG, Gmunder Strasse 37-37a, 81379 München, Germany or are taken from the following citations:

a) J.D. White et al., JACS 2003, 123, 5407-5413.
b) S. Danishefsky et al., JACS 1997, 119, 10073-10092.
c) K.-H. Altmann, Mini Rev. In Med. Chem., 2003, 3, 149-158.
d) T.-T. Yang et al., Anal. Biochem. 1996, 241, 103-108.

Data for some epothilone derivatives with a replacement of the carbonyl moiety at the 5-position against a sulfoxide are shown in the following table. It could be demonstrated that a

replacement of the carbonyl function by SO results in epothilones with a better or similar activity range against certain cancer cell lines.

Epothilone with SO at 5-position	IC50 (nM)	Epothilone with CO at 5-position	IC50 (nM)
Thia-Epo D 	1.1-3.0 MCF-7	Epo D 	2-5 MCF-7
Thia-Epo B 	0.1-0.2 MCF-7 0,4-1,5 KB-31	Epo B 	0,42 MCF-7 0,19-1,2 KB-31
	0.2-0.9 MCF-7		0.5-1.0 MCF-7

These experimental data show that replacing the carbonyl function by a sulfide or a sulfone function results in epothilone derivatives having a similar activity against certain cancer cell lines.

I further declare, that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that wilful false statements are punishable by fine or imprisonment, or both, under section 1001 of title 18 of the US Code, and that such wilful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATE AND SIGNATURE

Martinsried, 30.04.2008